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ORIGINAL ARTICLE

Thrombolysis with tenecteplase in acute ischaemic stroke in a tertiary care setting in Sri Lanka: A retrospective study

Kishara Gooneratne[3], Lakmal Vithanage[1], Ishanka Talagala[3], Niroshan C Lokunarangoda[3], Nilantha Gamage[1], Nishantha P Muthumal[1], Aruna Rodrigo[1], Jagath Kosgahakumbura[1], Gimhani Liyanage[3], Amandi Perera[2], Udaya K Ranawaka[4]

[1]District General Hospital Hambantota, Sri Lanka.

[2]National Hospital of Sri Lanka, Colombo, Sri Lanka.

[3]Faculty of Medicine, University of Moratuwa, Sri Lanka.

[4]Department of Clinical Medicine, Faculty of Medicine, University of Kelaniya, Sri Lanka.

Correspondence

Kishara Gooneratne

Faculty of Medicine, University of Moratuwa, Sri Lanka.

E-mail: kishig@gmail.com

https://orcid.org/0000-0003-3373-0432

Abstract

Introduction: Alteplase (ALT) is the standard thrombolytic treatment in acute ischaemic stroke (AIS). Tenecteplase (TNK) is proven to be effective in acute coronary syndrome, is relatively cheap, widely available and can easily be given as a single intravenous (IV) bolus. Despite evidence for its use, there is equivocal guidance for the use of TNK in AIS. On the background of a global reduction in stroke admissions, treatment interventions and prolonged treatment time metrics due to the COVID-19 pandemic, this study highlights the experience with TNK in a tertiary care setting in Sri Lanka, during the pandemic.

Objectives: To describe the outcomes at 48 hours among stroke patients who underwent thrombolysis with TNK at District General Hospital Hambantota, Sri Lanka over a period of one year.

Methods: We retrospectively reviewed records of adults with AIS thrombolysed with 0.25 mg/kg TNK. The National Institutes of Health Stroke Scale (NIHSS) was assessed on admission and at 24-hours following treatment. Patients were observed for 48-hours for potential adverse events.

Results: We thrombolysed 20 consecutive patients over one-year. The baseline mean NIHSS was 9.7 (standard deviation (SD)=4.4; range 4-22), and the 24h-post thrombolysis mean NIHSS was 6.0 (SD=7.3; range 0-28). Seventy percent (n=14) showed an improved NIHSS of at least 1-point after thrombolysis (mean difference=3.7; SD=6.46), and 55% (n=11) displayed a major clinical improvement (change in NIHSS ≥ 4). Ten percent (n=2) developed major adverse effects (one intra-cranial haemorrhage; one haemorrhagic transformation). There were no deaths.

Conclusions: TNK 0.25mg/kg for the treatment of AIS appeared efficacious and safe in our case series. The limitation in this study was the low number of patients who underwent thrombolysis during the study period, as a probable effect of the COVID-19 pandemic. Thrombolysis with TNK could be a cost-effective alternative to alteplase in resource-limited South Asian settings.

KEYWORDS

Acute stroke outcomes, stroke management in Sri Lanka, South Asia

INTRODUCTION

Tenecteplase (TNK) is a genetically modified form of human tissue plasminogen activator (tPA).[1] Alteplase (ALT), which is a recombinant tPA, is recommended as the standard treatment for thrombolysis in acute ischaemic stroke (AIS) in most of the international guidelines.[2] TNK is an established treatment for acute coronary syndrome (ACS) where, in head-to-head trials against ALT, it has shown equal therapeutic efficacy and fewer major bleeding complications.[3] TNK has several presumed advantages over ALT in the treatment of AIS:[4,5] (1) higher fibrin specificity, with less haemorrhagic complications, (2) greater resistance to plasminogen activator inhibitor-1 that may possess higher efficacy in clot lysis, and (3) longer serum half-life, allowing for single bolus administration. Further, TNK is more cost-effective [6] and more widely available owing to its widespread use in the management of ACS. These are added advantages over ALT in the treatment of patients with AIS, especially in low resource settings such as Sri Lanka. There is currently no clear guidance in most international guidelines on the use of TNK over ALT in the management of AIS.[2,7] However, some healthcare systems[8] have switched to TNK from ALT based on increasing trial safety data and endorsement in some recent guidelines.[9]

The impact of COVID-19 on stroke care has been significant with a global decline of approximately 19%, in stroke related hospitalization.[10] This was similar in Asia with a reported decline of approximately 20%.[10] There was also a 13% reduction in intravenous thrombolysis rates reported during this period.[11]

This study highlights the experience with the use of TNK in Sri Lanka, a lower middle-income country in South Asia, during the COVID pandemic and provides insight into its efficacy and safety profile.

METHODS

We retrospectively reviewed records of adults who underwent thrombolysis using TNK at District General Hospital, Hambantota, over a 13-month period from July 2020 to July 2021. Hambantota district in the Southern Province of Sri Lanka has a population around 600,000.[12] Nearly 96% of the population is considered to be rural.[12] The District General Hospital Hambantota is the only tertiary care hospital providing services to the above population.

The Ministry of Health in Sri Lanka does not provide specific guidance for thrombolysis in AIS. Consensus agreement from key stakeholders in emergency, medical, and pharmacology departments within the hospital provided endorsement for a practice change to the use of TNK in AIS during the COVID-19 pandemic (ALT was not used during this period). This decision was supported by the off-label use of TNK in other parts of the world and its recommendation in certain international guidelines.[8,9]

All patients admitted with AIS to the hospital were screened for their eligibility for intravenous thrombolysis at the emergency treatment unit. A non-contrast computed tomography (CT)-brain scan was done on admission, and baseline National Institutes of Health Stroke Scale (NIHSS) examination was performed. All eligible patients during the study period were selected for the study using pre-defined inclusion and exclusion criteria (supplementary file) and informed written consent was obtained from the patients (or proxy consent obtained from a relative or a caregiver for patients unable to provide consent due to neurological deficits). TNK was administered as a single intravenous bolus (over 5-10 seconds) at a dose of 0.25 mg/kg (not exceeding 25mg). Follow-up imaging with a CT-brain was performed at 24-48 hours and the NIHSS score was reassessed at 24-hours. Major clinical improvement was defined as a change in NIHSS ≥4 at 24 hours. The number of patients who achieved major clinical improvement and associations for such improvement were assessed using chi square tests at $p < 0.05$ significance level. Adverse events such as symptomatic intracranial haemorrhage within 48-hours (increase in NIHSS as a result of haemorrhage), asymptomatic intracranial haemorrhage (no change in NIHSS) (identified by repeated brain imaging), systemic bleeding and death from any cause were recorded.

RESULTS

A total of 20 patients were thrombolysed [males 80%; age range 37-84 years; mean age 64.5 years (SD=11.03)]. Frequency distribution of stroke patients with age are depicted in Figure 1. The mean time duration from symptom onset to thrombolysis was 162.3 minutes (standard deviation (SD)=66.74; range 70.0-270.0 minutes). The duration from the admission to administration of TNK (door-to-needle time) ranged from 30.0 minutes to 100.0 minutes, with a mean delay of 55.8 minutes (SD=18.4). Frequency distribution of the patients based on the time duration from the point of onset of symptoms to treatment are shown in Figure 2. Large vessel occlusion was observed among 75% (n=15) of the patients. The demographic and clinical details of the thrombolysed patients are given in Table 1.

The mean baseline NIHSS was 9.7 (SD=4.4; range 4.0-22.0). However, the mean NIHSS improved to 6.0 (SD=7.3) at 24-hours following thrombolysis (range 0.0 to 28.0). This mean difference of NIHSS scores on admission and 24-hours following thrombolysis was statistically significant (paired t=2.559; df=19; p=0.019). Fourteen patients (70%) showed an improved NIHSS by at least 1-point following thrombolysis (mean difference=3.7; SD=6.46); 15% (n=3) showed no improvement, and 15% (n=3) deteriorated. Importantly, 55% (n=11) of the patients displayed a major clinical improvement (NIHSS ≥4).

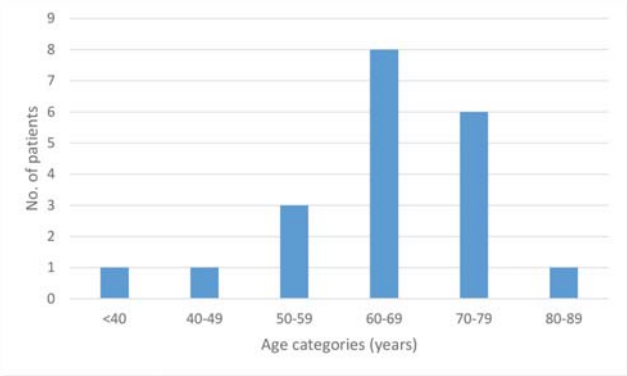

FIGURE 1 **Frequency distribution of stroke patients with age category.**

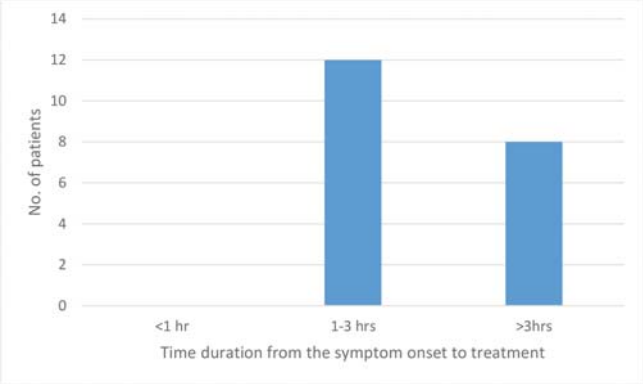

FIGURE 2 **Frequency distribution of the patients based on the time duration from the point of onset of symptoms to treatment.**

TABLE 1 Details of patients who underwent thrombolysis

Patient No	Age	Sex	NIHSS (on admission)	NIHSS 24h	Time from symptom onset (mins)	Door to needle time
1	75	M	13	17	90	50
2^	52	M	14	2	210	60
3^	59	F	6	0	120	60
4	65	M	7	4	150	30
5	72	M	7	5	90	35
6^	63	M	5	1	225	60
7[a]	76	M	16	16	120	60
8^	67	M	7	0	230	100
9	78	F	15	28	100	90
10	65	M	11	8	120	35
11[b,c]	62	M	22	2	70	30
12	49	M	11	12	225	45
13^	70	M	8	2	90	60
14[a,b]	73	F	9	1	270	75
15	84	F	8	8	240	55
16^	53	M	9	2	225	65
17^	60	M	7	2	150	55
18	65	M	9	9	115	65
19^	65	M	4	0	270	40
20^	37	M	6	1	135	45

^Patients with major clinical improvement defined as NIHSS ≥4

Adverse events

[a] Patient 7 and 14 developed intracranial haemorrhages (ICH). They were not on antiplatelet therapy and had diabetes.

[b] Patient 11 and 14 developed cerebral oedema with established Middle Cerebral Artery territory infarction, with patient 14 requiring a craniotomy

[c] The disease course in Patient 11 was complicated by aspiration pneumonia

Major clinical improvement (NIHSS > 4) following thrombolysis was associated with age (≥ 65 years) (X^2= 5.690; df=1; p=0.017). There was no association of clinical improvement with gender (X^2=0.051; p=0.822), time from symptom onset to thrombolysis (X^2=2.155; p=0.142), or the door to needle time (X^2=1.818; p=0.178).

Two patients (10%) developed major adverse events following thrombolysis. One had an asymptomatic intracranial haemorrhage, and the other, haemorrhagic transformation of an established middle cerebral artery (MCA) territory infarct complicated by cerebral oedema (malignant MCA infarct). There were no deaths.

DISCUSSION

Our study highlighted the experience of the use of TNK in AIS in a tertiary care setting in Sri Lanka. The study showed that most patients displayed major clinical improvement following thrombolysis with TNK administered as a single intravenous bolus at a dose of 0.25 mg/kg. To our knowledge, this is the first data on the use of TNK in AIS from Sri Lanka.

South Asia has a disproportionate share of the global burden of stroke, accounting for >40% of global stroke deaths.[13] The incidence of stroke is expected to rise in the region, predominantly owing to an increasing aged population and due to economic growth and a resultant increase in stroke risk factors. Furthermore, mortality and disability following stroke is likely to be higher owing to insufficient healthcare facilities providing optimum care, in the region.[13] Availability of time dependent hyper-acute stroke care, including thrombolysis, is limited in South Asia, and cost-effective acute interventions may have a large impact on stroke outcomes in these resource-limited settings.[14]

A systematic review on the use of TNK in AIS by Burgos and Saver (2019) showed non-inferiority of TNK compared to ALT.[15] This review included 5 randomized trials, with mean age of patients being 70.8 years. The mean NIHSS score at baseline was 7 and mean time duration from symptom onset to treatment was 148 minutes. In contrast, our patient cohort had greater stroke severity at presentation (mean NIHSS 9.7) and had longer delays to thrombolysis from symptom onset (mean delay of 162.3 minutes). The impact of the pandemic impeding timely access to healthcare services may have been a factor to explain the latter.[15] Furthermore, District General Hospital Hambantota is a tertiary care institution situated in rural Sri Lanka. This fact may also explain the greater mean pre-hospital delay.

Heterogeneity between studies makes it difficult to draw meaningful conclusions regarding many aspects of the use of TNK in AIS, such as the optimal dosage, safety profile, and the benefit in different populations. As examples, the proportions of patients with large-vessel occlusion ranges from 47% to 100%;[13] while it was 75% in our series; various TNK doses have been used in studies including 0.1 mg/kg, 0.25 mg/kg, 0.32 mg/kg and 0.4 mg/kg.[15,16] We used 0.25mg/kg dose, which had shown maximum efficacy in several trials.[16,17] Improvement of the NIHSS ≥4 at 24 hours has been reported in 32%-71% of patients while it was 55% in our case series. Adverse events have been variable among trials. Intracerebral haemorrhage (ICH) rates ranged from 4%-15% irrespective of dose.[16] We experienced a 10% ICH rate. Mortality at 3 months has ranged from 5% to 17% in previous studies;[16] while no deaths were observed in our series, possibly due to the lack of long-term follow-up data and limited sample size. Though mortality rates cannot be compared due to the aforesaid reason, a major concern following thrombolysis is intracranial hemorrhage which can occur shortly after treatment and is a critical cause of early mortality. In the EXTEND-IA TNK and NOR-TEST trials, the primary concern for mortality was seen within the first 7 to 30 days. This was due to the acute nature of stroke and its immediate complications such as haemorrhage.[16]

Our study found TNK to be beneficial among patients ≥65 years of age. In the Norwegian TNK Stroke Trial in which there were 273 patients ≥80 years, the proportion of patients with excellent functional outcome was 44.1% with TNK vs 34.4% with ALT, however, this difference was not statically significant.[18] This may suggest TNK to be efficacious in older age patients.

Data on the use of thrombolysis in Sri Lanka are sparse. A single-centre study (n=89) on the use of ALT in AIS reported 57.3% of patients to be independent (Modified Rankin scale-0-2) at 3-months and an ICH rate of 12.4%.[19] These findings are similar to our case series.

Comparative data on the use of TNK or ALT in other regions of South Asia are limited. A small study of 14 patients from India[6] which used 0.2mg/kg TNK, quoted 64% with major clinical improvement (NIHSS ≥4) at 24 hours. They had a similar door to needle time and a similar proportion of large artery strokes. Another prospective observational study of 19 stroke patients treated with TNK in India found similar improvements in NIHSS scores however with lesser delay to thrombolysis from symptom onset (126 minutes).[20] The lack of large-scale studies in the region may be due to the scarcity of centres capable of thrombolysis in South Asia (only about 150 centres)[21] and the cost of ALT limiting its widespread usage.

Rates of thrombolysis remain low globally and more so in low and middle-income countries.[22] Patients from such countries experience stroke 15 years earlier compared to high-income countries, with individuals in the most productive phase of their lives being affected.[23] Many barriers in these countries prevent early administration of thrombolytic therapy, of which accessibility and affordability of ALT is one.[22] In a study by Nepal et al. only 20% of AIS patients reached the hospital

within the thrombolytic window period; and among them, 35% were denied thrombolysis because ALT was not affordable despite reaching the hospital on time.[24] Thus, our study highlights that TNK, which is cost-effective[24] and easier to administer[22] can be considered as a safe and effective alternative to the standard ALT in patients with AIS, especially in the resource poor settings of low and middle income countries such as Sri Lanka.

LIMITATIONS

The limitations of our study include the small sample size which impedes generalisability of our findings, and lack of data on long-term follow-up. Such limited numbers may be a result of; limitations in access to healthcare, deficiencies in identifying stroke and effects of the pandemic resulting in hospital avoidance.[26] During the pandemic there were delays in presentation to hospital globally (increase in delay of nearly 21%).[27] This was attributed to shelter in place advisories or patient fear of presentation and COVID-19 associated precautions.[27] Such factors could have negatively impacted the number reaching hospital within the window period for thrombolysis in our cohort.

CONCLUSION

TNK at a dose of 0.25mg/kg for the treatment of patients with AIS was found to cause a significant improvement of the NIHSS score and was safe in our study of Sri Lankan patients, in the short term, falling within the ranges reported in published randomised controlled trials to date. TNK can be a cost-effective alternative in the South Asian rural setting. Long term follow-up data are recommended to assess the long-term efficacy and safety of TNK in treating patients with AIS.

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THE SUPPLEMENTARY DATA

Inclusion Criteria

- Male and female patients ≥ 18 years of age
- Patients who are diagnosed of AIS with measurable deficits on the National Institutes of Health Stroke Scale (NIHSS) 4-25.
- Patients with AIS admitted within 4.5 hours of symptom onset which refers to 'last known to be well'

Exclusion Criteria

- Patients with haemorrhage on non-contrast computer tomography (NCCT) scan
- Wake up strokes in which time of onset of neurological deficit cannot be accurately gauged

- ***Absolute contraindications***
    - History of severe head trauma or stroke within 3 months
    - Suspected subarachnoid hemorrhage
    - Arterial puncture at a non-compressible site within the previous 1 week
    - History of intracranial hemorrhage
    - Intracranial tumor, vascular malformation, or arterial aneurysm
    - Recent intracranial or intraspinal surgery
    - Systolic blood pressure ≥180 mm Hg, or diastolic blood pressure ≥ 100 mm Hg; Increased blood pressure
    - Active internal bleeding
    - Acute bleeding tendency, including platelet count below 100×10^9/L or otherwise
    - Heparin treatment was performed within 48 h (APTT exceeded the upper limit of normal range)
    - Warfarin has been taken orally, and international normalized ratio (INR) is > 1.7 or prothrombin time (PT) > 15s
    - Anticoagulant drugs such as thrombin inhibitor or Xa factor inhibitor, argatroban (including new anticoagulants with unclear mechanism) are currently being used, and various sensitive laboratory tests are abnormal (such as live) APTT, INR, Platelet count, Serpentine ECT of pulse enzyme setting time; thrombin time TT or appropriate determination of Xa factor activity)
    - Blood glucose < 2.7 mmol/L
    - CT showed multilobular infarction (low density > 1 / 3 cerebral hemisphere)

- ***Relative contraindications:*** The risks and benefits of thrombolysis were carefully considered and weighed in the following cases (that is, although there is one or more relative contraindications, it was not considered as absolutely impossible to thrombolysis)
    - Mild stroke or stroke with rapid improvement of symptoms
    - Women in pregnancy
    - Symptoms of neurological impairment after seizures
    - There have been major surgical operations or serious injuries in the last 2 weeks
    - There were gastrointestinal or urinary system bleeding in recent 3 weeks
    - History of myocardial infarction within 3 months